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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/578,534	05/24/2000	David C. Crossman	MSA-017.02	5359

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EXAMINER	
MYERS, CARLA J	

ART UNIT	PAPER NUMBER
1634	20

DATE MAILED: 11/18/2002

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No. 09/578,534	Applicant(s) CROSSMAN ET AL.	
	Examiner Carla Myers	Art Unit 1634	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *19 August 2002* .

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-79* is/are pending in the application.

4a) Of the above claim(s) *8-76* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-7* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s) *12, 13* .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other:

1. This action is in response to Paper No. 19, filed August 19, 2002. Applicants amendments and arguments presented in the response of Paper No. 19 have been fully considered but are not persuasive to overcome all grounds of rejection. All rejections not reiterated herein are hereby withdrawn. This action is made final.

2. This application contains claims 8-76 drawn to an invention nonelected with traverse in Paper No. 9. A complete reply to the final rejection must include cancellation of nonelected claims or other appropriate action (37 CFR 1.144) See MPEP § 821.01.

3. Claims 1-7 and 77-79 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for methods for determining whether a SVD patient has or is predisposed to developing arterial restenosis wherein the methods comprise detecting the presence of IL-1RN (VNTR) allele 1 as indicative of a predisposition to arterial restenosis in SVD patients, does not reasonably provide enablement for methods for determining whether a subject has or is predisposed to developing restenosis wherein said methods detect any other alleles in the IL-1 gene cluster, including IL-1A (+4845), IL-1B (-511) or IL-1B (+3954). The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to practice the invention commensurate in scope with these claims.

The following factors have been considered in formulating this rejection (*In re Wands,* 858F.2d 731, 8 USPQ2d 1400 (Fed. Cir. 1988): the breadth of the claims, the nature of the invention, the state of the prior art, the relative skill of those in the art, the predictability or

unpredictability of the art, the amount of direction or guidance presented, the presence or absence of working examples of the invention and the quantity of experimentation necessary.

The specification identifies a number of IL-1 alleles, including IL-1RN(+2018), IL-1RN (VNTR), IL-1A (+4845), IL-1B(-511) and IL-1B(+3954). The specification (page 66-67) teaches that the IL-1RN (VNTR) allele 2 is associated with a lower restenosis rate in patients with SVD. Accordingly, the specification has enabled methods for determining whether an SVD patient has or is predisposed to developing restenosis wherein the methods comprise detecting the IL-1RN (VNTR) allele 1 as indicative of an increased likelihood of having or being predisposed to restenosis. However, the specification also teaches that no significant association was found between the occurrence of IL-1RN(VNTR) allele 2 and restenosis in MVD patients (see page 66 and Table I). This finding clearly emphasizes the unpredictability in the art of establishing a correlation between IL-1 alleles and the occurrence of disorders associated with cardiovascular disease in that the results obtained with one type of population (SVD patients) cannot be extrapolated to other populations (e.g., MVD patients). Accordingly, the specification is not enabling for methods in which restenosis is diagnosed in non-SVD patients, particularly in MVD patients. There is no universal association between the presence of alleles in the IL-1 gene cluster and the occurrence of restenosis. The art has not established a correlation between any alleles of IL-1 and the occurrence of restenosis which would allow for a general relationship to be established between the presence of an IL-1 gene cluster allele and any cardiovascular disease. In addition, the specification has not taught any particular attribute of the IL-1RN (VNTR) allele

that could be extrapolated to other alleles in order to predictably identify other alleles in these genes and other IL-1 genes or any other unstated gene which would be predictive of restenosis. The specification further postulates that alleles in linkage disequilibrium with IL-1 alleles can be used to determine susceptibility to disease. Yet, the specification (page 66) states that "(t)he Mantel-Haenzel results summarized over the Leicester and Sheffield cohorts showed no significant differences in genotypic distributions at the IL-1A (-889), IL-1B (+3954), and IL-1B (-511) loci between restenosers and non-restenosers (Table II)". Accordingly, alleles which are considered to be in linkage disequilibrium with IL-1RN (VNTR) were found to show no correlation with restenosis. This finding also underlies the unpredictability in the art of cardiovascular disease diagnosis in that it clarifies that there is not a universal association between IL-1 alleles and the occurrence of restenosis and that it is highly unpredictable as which additional alleles, if any, could be used to determine susceptibility to restenosis. Additional evidence of the unpredictability in the art of establishing a correlation between IL-1 alleles and restenosis is found in the specification which provides teachings which are directly contradictory to the findings set forth on pages 66 and 67 of the specification. In particular, page 88 of the specification states that "allele 2 of the 4845, -511, +3954 and VNTR markers in the IL-1RN gene will be over-represented in restenosis". Yet, claims 2 and 77-79 are drawn to methods in which the presence of **allele 1** of IL-1A (+4845), IL-1B (-511), IL-1B (+3954) and IL-1RN (+2018) are detected as indicative of the presence of or predisposition to restenosis. It is requested that Applicants provide an explanation regarding these conflicting teaches in the

specification. The findings presented in parent application 09/431,352 further establish the unpredictability of using alleles in linkage disequilibrium as a means for diagnosing susceptibility to cardiovascular disease. For example, the '352 specification teaches that other alleles in the haplotype containing allele 2 of IL-1RN (VNTR), IL-1RN (+2018) and IL-1A (-511) are not correlated with single vessel coronary artery disease. The specification at page 83 states that "(t)here was no significant difference between the control and the diseased patients in the frequency of the different alleles in the genes for IL-1A (-889 marker), IL-1B (+3954 marker), or TNFα (-308 marker)". Since even alleles in linkage disequilibrium with allele 2 of IL-1RN (VNTR), IL-1RN (+2018) and IL-1A (-511) are not correlated with single vessel coronary artery disease, there is no predictable means for determining which of the multitude of known and unknown alleles of IL-1 genes and other genes would be associated with a cardiovascular disease such as restenosis and additional alleles could only be identified by one of skill in the art through extensive trial and error experimentation. The specification at page 84 of '352 also teaches that IL-1B (-511) allele 2 is present in 54% of patients with multiple coronary artery disease, versus 38% of control patients. The specification (page 85) further states that "(t)here was no significant difference between the control and diseased patients in the frequency of different alleles in the genes for IL-1A (-889 marker), IL-1B (+3954 marker), and IL-1RN (VNTR marker)". This result indicates that alleles characterized in the specification of '352 as being in linkage disequilibrium with IL-1B (-511) allele 2 are not in fact correlated with the occurrence of multiple coronary artery disease, thereby further establishing the unpredictability

of using alleles in linkage disequilibrium with IL-1 alleles as diagnostic markers for cardiovascular disease. Case law has established that "(t)o be enabling, the specification of a patent must teach those skilled in the art how to make and use the full scope of the claimed invention without 'undue experimentation." *In re Wright* 990 F.2d 1557, 1561. *In re Fisher,* 427 F.2d 833, 839, 166 USPQ 18, 24 (CCPA 1970) it was determined that "(t)he scope of the claims must bear a reasonable correlation to the scope of enablement provided by the specification to persons of ordinary skill in the art". Furthermore, the Court in *Genetech Inc. v Novo Nordisk* 42 USPQ2d 1001 held that "(I)t is the specification, not the knowledge of one skilled in the art that must supply the novel aspects of the invention in order to constitute adequate enablement". In the instant case, the specification has identified only one allele , IL-1RN (VNTR) allele 1, which may be useful for diagnosing susceptibility to restenosis in SVD patients. Thereby, the scope of the claims does not bear a reasonable correlation to the scope of enablement provided by the specification and undue experimentation would be required to practice the full scope of the claims because this would require randomized searching of IL-1 genes and the entire genome for additional alleles which may show an association with restenosis. Again, the specification illustrates the unpredictability in establishing a correlation between an IL-1 alleles and the occurrence of cardiovascular disease in that the specification teaches that while one allele has been found to be correlated with restenosis, other alleles characterized as being in linkage disequilibrium with said allele are not correlated with restenosis. In addition, the specification clearly teaches that while one allele may be correlated with a particular type of cardiovascular

disease, that same allele may not be correlated with a different type of cardiovascular disease. The specification has not provided any specific data clearly establishing the occurrence of IL-1B (-511), IL-1B (+3954), IL-1B (+4845) alleles in restenosis and no working examples are provided in the specification in which these alleles have been successfully employed to determine the presence or predisposition to restenosis. Accordingly, in view of the lack of information in the specification as to how to reasonably identify other alleles correlated with restenosis without undue experimentation and in view of the unpredictability in the art in correlating the presence of an allele with a disease, particularly in correlating the presence of an IL-1 polymorphism with restenosis, the specification has not adequately taught one of skill in the art how to practice the claimed invention as it is broadly claimed.

Response to arguments:

In the response of Paper No. 19, Applicants state that "The fact that the Examiner has not found the results of all of the exemplary studies to her liking is not determinative to a finding of lack of enablement." This argument does not fairly characterize the rejection.. The rejection is not based on the examiner's personal opinion of the studies set forth in the specification. Rather, as detailed above, the rejection is based on the unpredictability in the art and the lack of guidance and evidence in the specification to support applicants contention that it would not require undue experimentation to identify additional IL-1 alleles associated with restenosis. Secondly, Applicants state that the "failure to find a statistically demonstrable association in one study of, e.g. limited sample size, is not determinative." However, at page 66 of the specification,

Applicants clearly state that "(t)he frequency of allele 2 IL-1RN (VNTR*2) was however increased in the non-restenosers." Applicants have provided no evidence to show that MVD patients do in fact demonstrate an association between the IL-1RN (VNTR) allele 2 and restenosis. If the only information provided in the specification indicates that allele 2 of IL-1RN (VNTR) is correlated with the lack of restenosis in MVD patients, how does one then draw the conclusion that allele 2 of IL-1RN (VNTR) predisposes MVD patients to restenosis?

Applicants state that the lack of a working example is not determinative of a finding of lack of enablement. This argument is not convincing because the rejection is not based solely on the lack of a working example. This is merely one point that was taken into consideration when analyzing the teachings of the specification and the breadth of the claims. As clearly set forth above, the following factors have been considered in formulating this rejection (*In re Wands,* 858F.2d 731, 8 USPQ2d 1400 (Fed. Cir. 1988): **the breadth of the claims, the nature of the invention, the state of the prior art, the relative skill of those in the art, the predictability or unpredictability of the art, the amount of direction or guidance presented, the presence or absence of working examples of the invention and the quantity of experimentation necessary**.

Applicants state that the "proper inquiry is whether one of skill in the art could have been able to practice the claimed invention (e.g. use of IL-1B (-511), IL-1B(+3954), IL-1B (+4845) polymorphic alleles to predict restenosis) without undue experimentation." However, this is not the proper inquiry because the claims are not limited to the detection of these alleles. Rather, the

majority of the claims have been amended to read broadly on methods for detecting any restenosis associated IL-1 allele as indicative that a subject has or is predisposed to the development of restenosis. Applicants assert that where an individual allele of a haplotype is associated with restenosis, then other alleles of the haplotype would also be associated with restenosis. Applicants cite Johnson in support of their arguments. However, the Johnson reference teaches general methods for scanning the human genome to identify polymorphisms. The present rejection does not question whether one of skill in the art would be capable of identifying additional polymorphisms in the IL-1 gene. The teachings of Johnson support the finding of the unpredictability in the art of establishing an association between a polymorphism and a disease and the quantity of experimentation required to establish a correlation between a polymorphism and a disease. As stated by Johnson "(i)f suitably powered studies that evaluate common variation fail to produce convincing associations, the multiple-rare-variants model of common disease will then need to be considered...Statistical tests that combine information from all of the rare variants f a gene may facilitate the detection [of] a disease locus comprised of several rare alleles...Studying haplotypes has two further advantages. If the disease association of a specific allele is dependent on *cis* interactions with other loci, the disease association may not be detected unless the functional haplotypic unit itself is analyzed. In addition, exploiting the differences in haplotype diversity and frequency between populations (trans-racial mapping) may be invaluable when attempting to pinpoint which variants are most likely to be the primary etiological determinants of common diseases." Accordingly, the teachings of Johnson do not

support Applicants contention that any individual member of a haplotype may be used to diagnose a disease. Rather, the teachings of Johnson indicate that the association between an allele or haplotype and a disease is complex, such that under some circumstances only the haplotype may be useful in predicting susceptibility to disease and the individual alleles alone may not be useful in predicting susceptibility to disease. Further, Applicants response does not address the specific examples set forth in the rejection in which Applicants own work has demonstrated that while one allele may be associated with a disease, alleles in linkage disequilibrium with that allele are often not associated with the disease.

4. The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. See *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970);and, *In re Thorington,* 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.32 (c) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent is shown to be commonly owned with this application. See 37 CFR 1.130(b).

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

Claims 1, 3, 4, 6 and 7 are rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 1-6 of U.S. Patent No. 6,268,142. Although the conflicting claims are not identical, they are not patentably distinct from each other because the instant claims and the claims of '142 are both inclusive of methods for determining a patient's predisposition to disease wherein the methods comprise detecting IL-1A (+4845), IL-1RN (+2018) or IL-1B (-511). It is noted that the claims of '142 are inclusive of methods for determining predisposition to any disease or condition associated with an IL-1 inflammatory haplotype, including cardiovascular disorders and thereby are inclusive of methods for detecting the cardiovascular disorder of arterial restenosis.

In the response of Paper No. 19, Applicants state that they will file a terminal disclaimer if the pending claims are found to be allowable. A terminal disclaimer has not yet been filed. Accordingly, the rejection is maintained for the reasons of record.

5. Claims 1-7 and 77-79 are rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 1-15 of U.S. Patent No.6,210,877. Although the conflicting claims are not identical, they are not patentably distinct from each other because the instant claims and the claims of '877 are both inclusive of methods for determining a patient's predisposition to disease wherein the methods comprise detecting IL-1RN (VNTR) or

IL-1B (-511). It is noted that the claims of '877 are inclusive of methods for determining predisposition to coronary artery disease and thereby are inclusive of methods for detecting the coronary artery disease of arterial restenosis.

In the response of Paper No. 19, Applicants state that the present claims are distinct over the claims of '877 because the present claims are directed to methods for predicting whether a subject is predisposed to developing restenosis, whereas the claims of '877 are directed to methods for predicting whether a subject is predisposed to coronary artery disease. This argument is not convincing because the claims of '877 appear to be inclusive of methods for predicting a predisposition to restenosis. The instant specification (page 20) defines cardiovascular disorder associated alleles as including alleles associated with restenosis. The specification also states that cardiovascular disease includes both coronary artery disease and peripheral vascular disease. Accordingly, as defined by the present specification, cardiovascular disorders and coronary artery disorders appear to include restenosis.

THIS ACTION IS MADE FINAL. Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR

1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Carla Myers whose telephone number is (703) 308-2199. The examiner can normally be reached on Monday-Thursday from 6:30 AM-5:00 PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, W. Gary Jones, can be reached on (703)-308-1152. The fax number for the Technology Center is (703)-872-9306 or (703)-872-9307 (after final).

Any inquiry of a general nature or relating to the status of this application should be directed to the receptionist whose telephone number is (703) 308-0196.

Carla Myers

November 13, 2002

Carla Myers
CARLA J. MYERS
PRIMARY EXAMINER